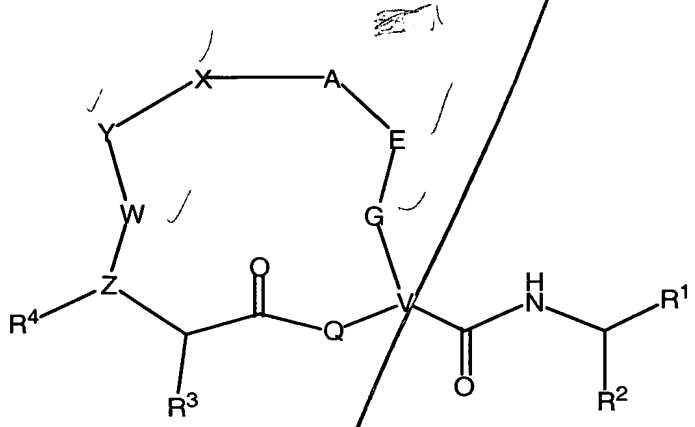
Claims

What is claimed is:

1. A macrocyclic compound, including enantiomers, stereoisomers, rotomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound having the general structure shown in Formula I:



Formula I

wherein:

E, X and Y may be independently present or absent, and if present are independently selected from the moieties: alkyl, aryl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, aryl ether, alkyl amino, aryl amino, alkyl-aryl amino, alkyl sulfide, alkyl-aryl sulfide, aryl sulfide, alkyl sulfone, alkyl-aryl sulfone, aryl sulfone, alkyl-alkyl sulfoxide, alkyl-aryl sulfoxide, alkyl amide, alkyl-aryl amide, aryl amide, alkyl sulfonamide, alkyl-aryl sulfonamide, aryl sulfonamide, alkyl urea, alkyl-aryl urea, aryl urea, alkyl carbamate, alkyl-aryl carbamate, aryl carbamate, alkyl -hydrazide, alkyl-aryl hydrazide, alkyl hydroxamide, alkyl-aryl hydroxamide, alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl or a combination thereof, with the proviso that E, X and Y may optionally be additionally substituted with moieties selected from the group consisting of aromatic, alkyl, alkyl-aryl, heteroalkyl, aryl-heteroaryl, alkyl-

heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, alkyl sulfide, alkyl-aryl sulfide, alkyl sulfone, alkyl-aryl sulfone, alkyl amide, alkyl-aryl amide, alkyl sulfonamide, , alkyl amines, alkyl-aryl amines, alkyl-aryl sulfonamide, alkyl urea, alkyl-aryl urea, alkyl carbamate, alkyl-aryl carbamate, halogen, hydroxyl amino, alkyl carbazate, aryl carbazate;

$R^1 = COR^5$ or $B(OR)_2$, wherein R^5 = H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, COR^7 wherein R^7 = H, OH, OR^8, CHR^9R^{10}, or NR^9R^{10} , wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})\ CONR^{12}R^{13}$, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, and R' are independently selected from a group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is selected from O, N, or CH;

W may be present or absent, and if W is present, W is selected from C=O, C=S, SO_2 or C=NR;

Q is $(NR)_p$, O, S, CH_2, CHR, CRR' or a double bond towards V;

A is O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_2 , C=O or a bond;

G is $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, NR, O, S, SO_2, $S(O)_2NH$, C=O, or a double bond towards E or V;

V is CH, CR or N;

p is a number from 0 to 6; and

R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl,

aryl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; heteroaryl; alkyl-aryl; alkyl-heteroaryl; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms;
with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamide, sulfoxide, sulfone, sulfonyl urea, hydrazide, hydroxamate and thiourea.

2. The compound of claim 1, wherein $R^1 = COR^5$, and R^5 is H, OH, $COOR^8$, or $CONR^9R^{10}$.

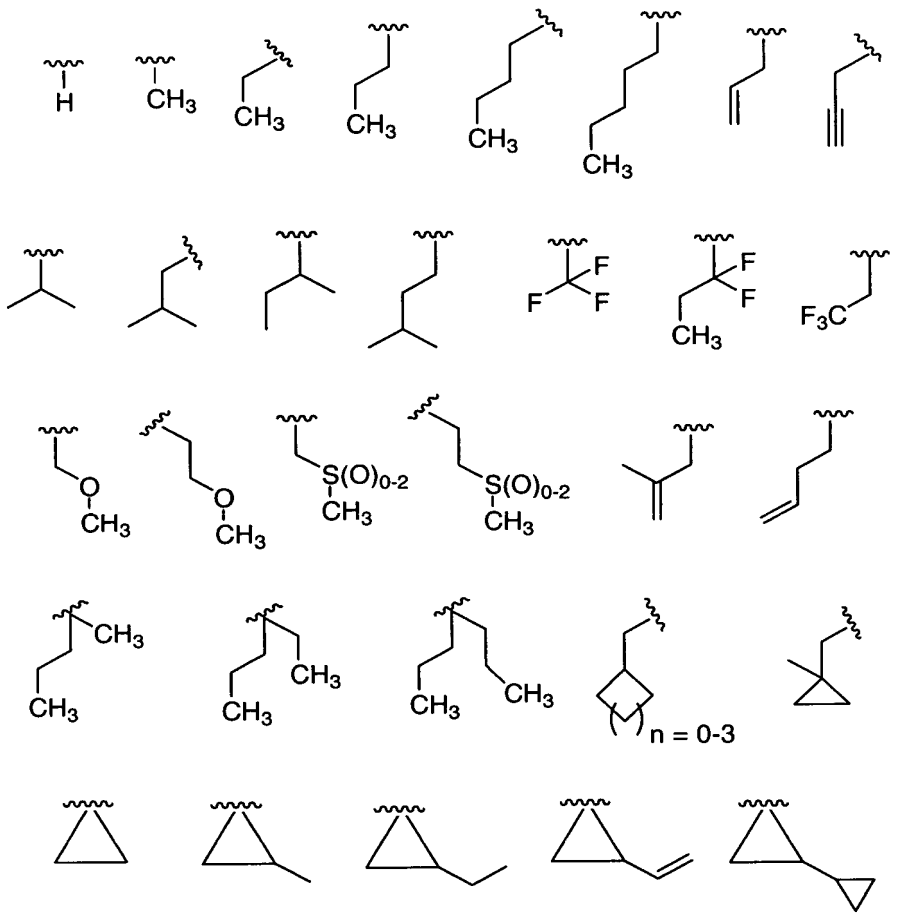
3. The compound of claim 2, wherein $R^1 = COCONR^9R^{10}$, and is R^9 is H, R^{10} is H, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})$ $CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$.

4. The compound of claim 3, wherein $R^{10} = CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein $R^{1'}$ is H or alkyl, and $R^{2'}$ is selected from the group consisting of phenyl, substituted phenyl, hetero atom-substituted phenyl, thiophenyl, cyclohexyl, cyclopentyl, cyclopropyl, piperidyl pyridyl and 2-indanyl.

5. The compound of claim 4, wherein $R^{1'}$ is H.

6. The compound of claim 5, wherein $R^{2'}$ = phenyl, thiophenyl, cyclohexyl, 2-indanyl, cyclopentyl, pyridyl, phenyl(4-$HNSO_2NH_2$), R^{11} is H or *tert*-butyl, R^{12} and R^{13} are methyl, and R' is hydroxymethyl or tert-butoxymethyl.

7. The compound of claim 1, wherein R^2 is selected from the group consisting of the following moieties:



8. The compound of claim 7 wherein R^1 = COR^5, and R^5 is H, OH, $COOR^8$, or $CONR^9R^{10}$.

9. The compound of claim 8 wherein V is CH.

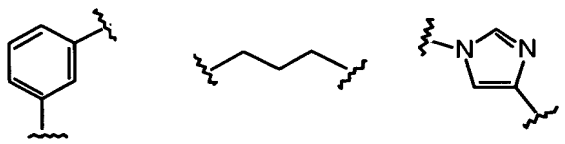
10. The compound of claim 9 wherein Q is NR or O.

11. The compound of claim 10 wherein G is CH_2.

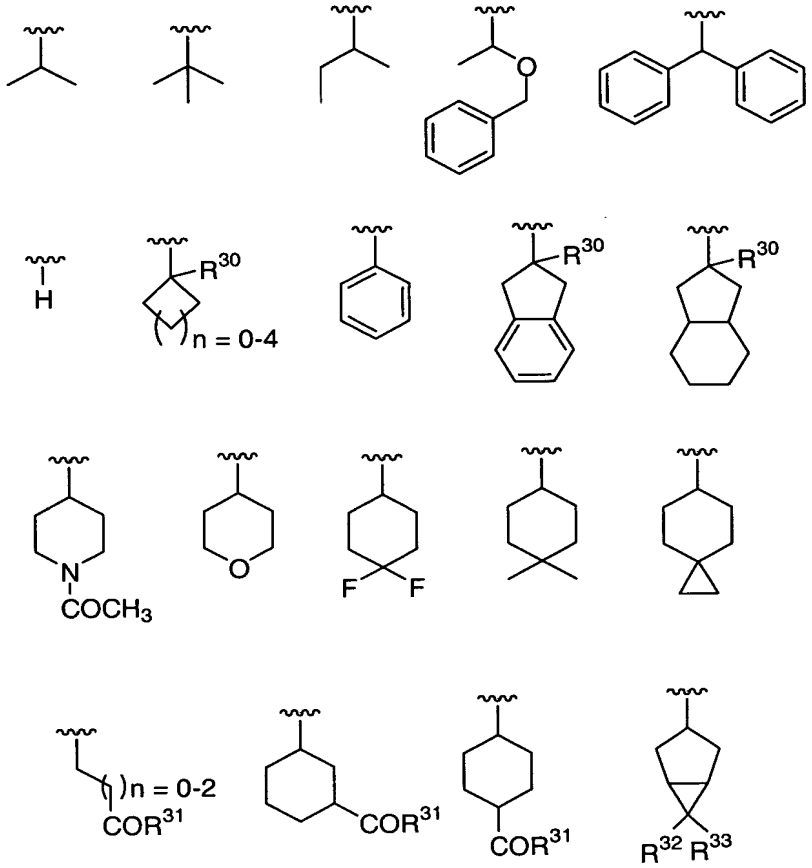
12. The compound of claim 11 wherein A is O, NR, CH=CH or CH_2.

13. The compound of claim 12 wherein E is alkyl, aryl, hereroalkyl, heteroaryl, alkyl, aryl, or cycloalkyl.

14. The compound of claim 13 wherein E is selected from the group consisting of the moieties:



15. The compound of claim 14 wherein R^3 is selected from the group consisting of the moieties:



wherein R^{30} = H, CH_3 or other alkyl groups;

R^{31} = OH, O-alkyl, NH_2, N-alkyl; and

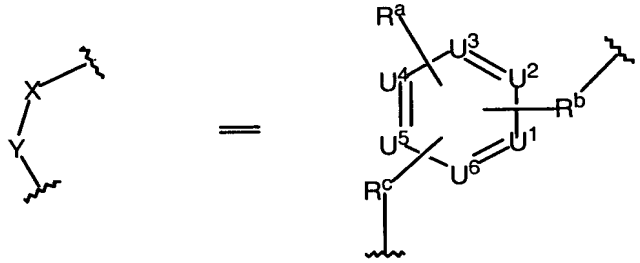
R^{32} and R^{33} may be the same or different and are selected independently from H, F, Cl, Br and CH_3.

16. The compound of claim 15 wherein Z = N and R^4= H.

17. The compound of claim 16 wherein W is C=O.

18. The compound of claim 17 wherein the moiety X-Y is selected from the group consisting of: C1-C10 alkyl, alkyl, cycloalkyl, heteroalkyl, arylalkyl, aryl, hereroaryl and alkylaryl.

19. The compound of claim 18, wherein:



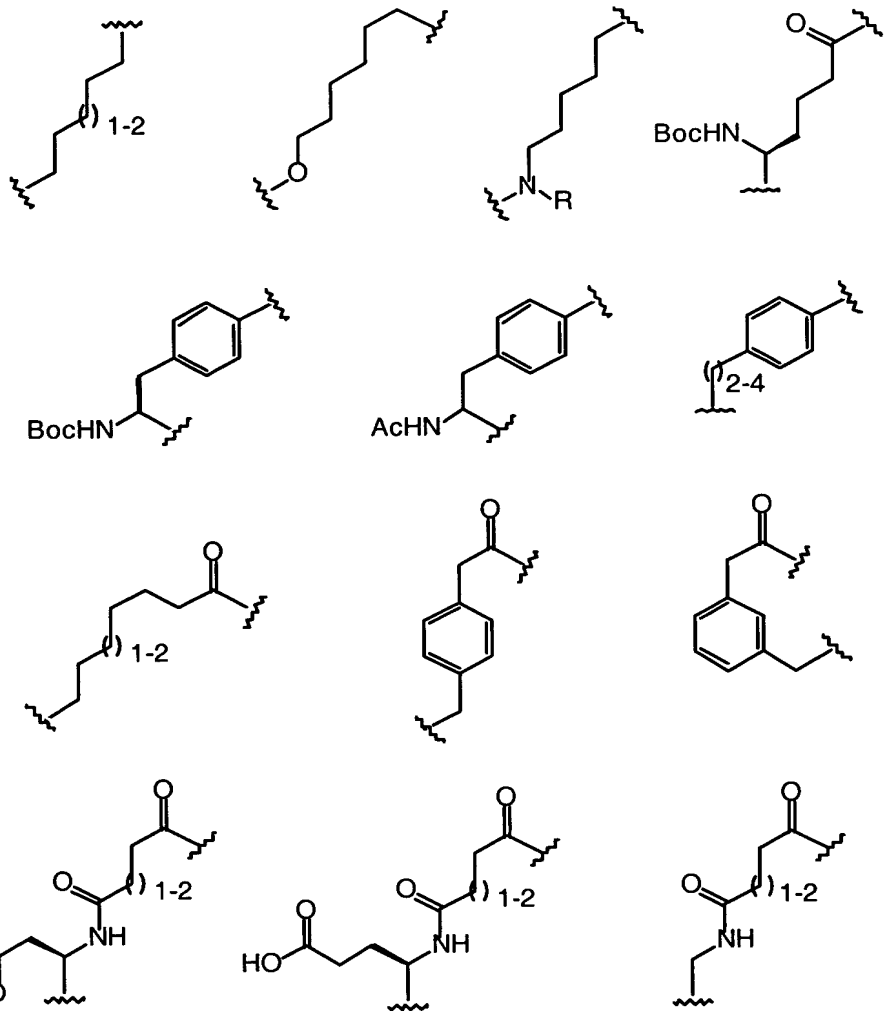
wherein R^b is connected directly to A and R^c is connected directly to W; and the moiety U^1, U^2, U^3, U^4, U^5 and U^6 form either a six membered carbon ring, or a five or six membered ring with one or more heteroatoms;

R^a = H, alkyl, alkoxy, hydroxy, alkylthio, halogen, nitro, cyano, carboxylic acid, ester, amide, amino, nitrile, or CF_3;

R^b is a bond, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, O, S, SO_2, NH, O(alkyl), S(alkyl), SO_2(alkyl) or N(alkyl); and

R^c is a bond, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, O, S, SO_2, NH, O(alkyl), S(alkyl), SO_2(alkyl), N(alkyl) or CH_2-N(alkyl) with the CH_2 being linked to the aromatic ring.

20. The compound of claim 18 wherein the moiety X-Y is selected from the group consisting of the following structures:



21. A pharmaceutical composition comprising as an active ingredient a compound of claim 1.

22. The pharmaceutical composition of claim 21 for use in treating disorders associated with Hepatitis C virus.

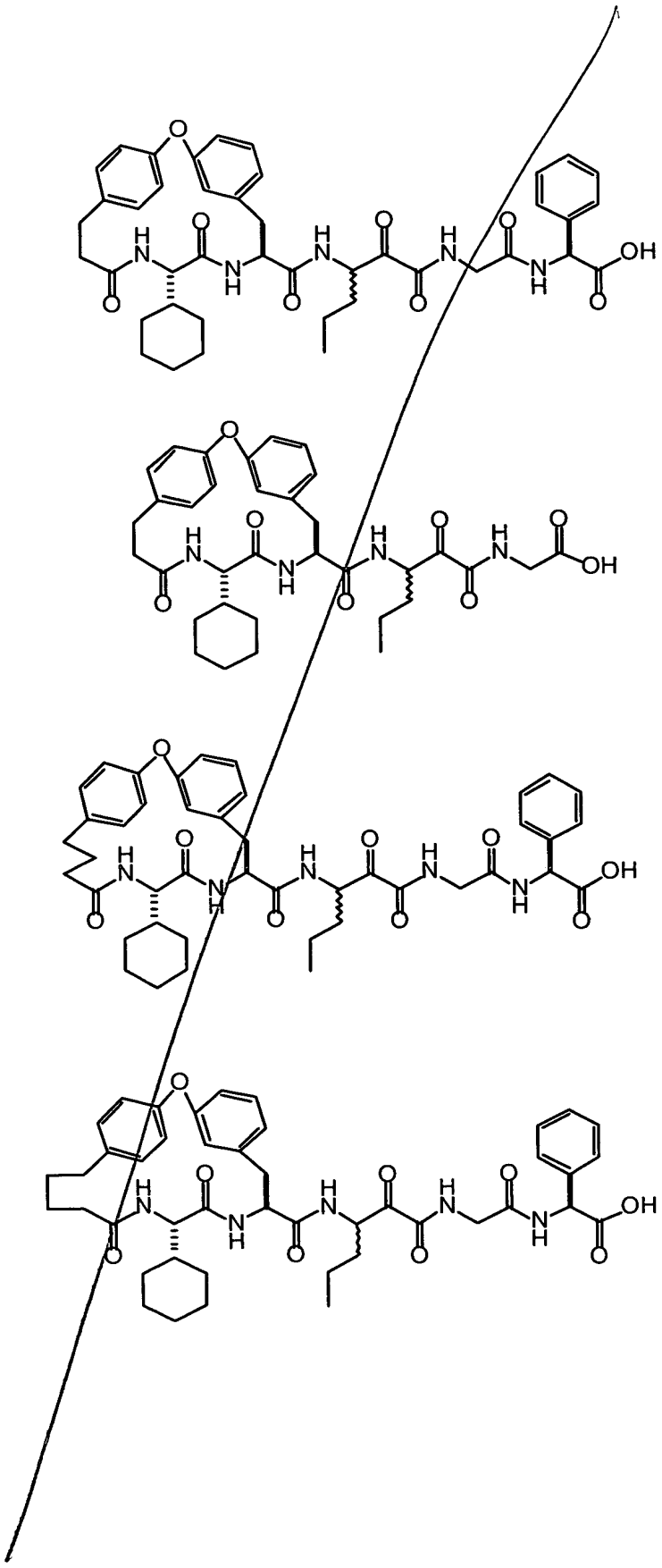
23. The pharmaceutical composition of claim 21 additionally comprising a pharmaceutically acceptable carrier.

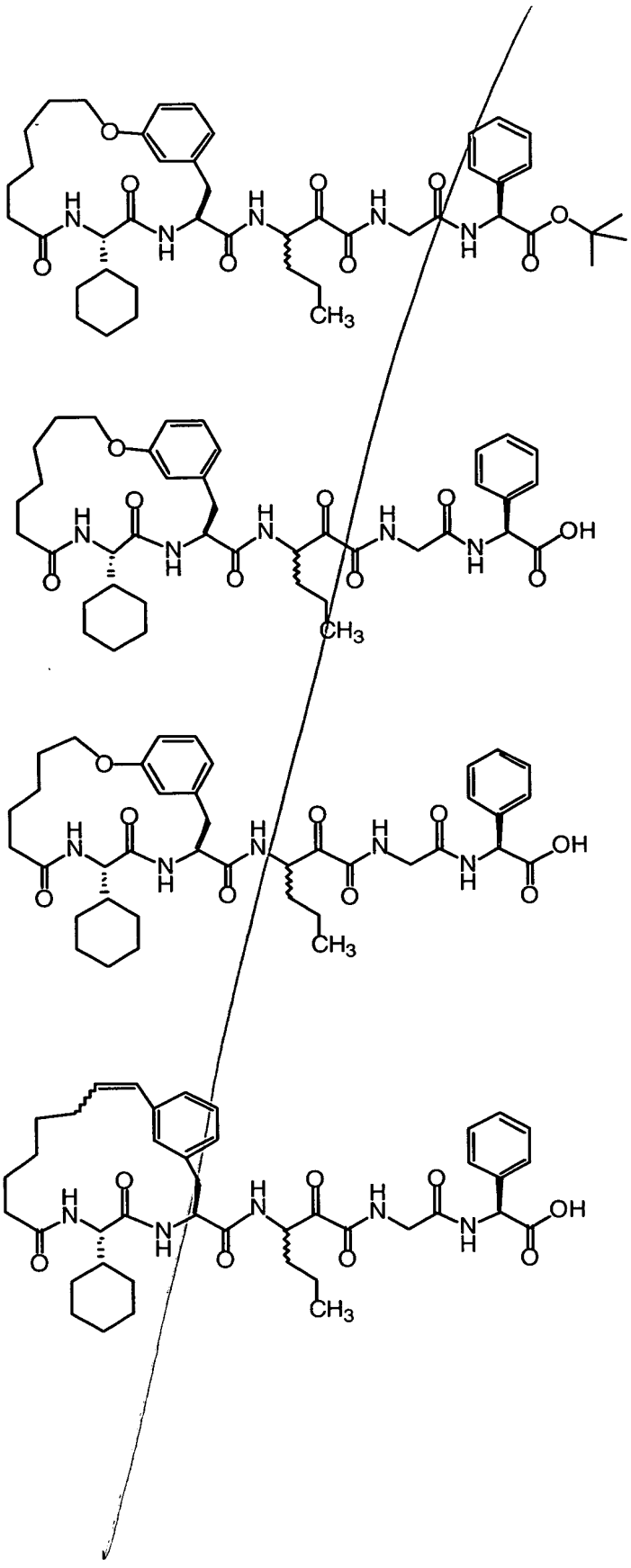
24. A method of treating disorders associated with the HCV protease, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which composition comprises therapeutically effective amounts of a compound of claim 1.

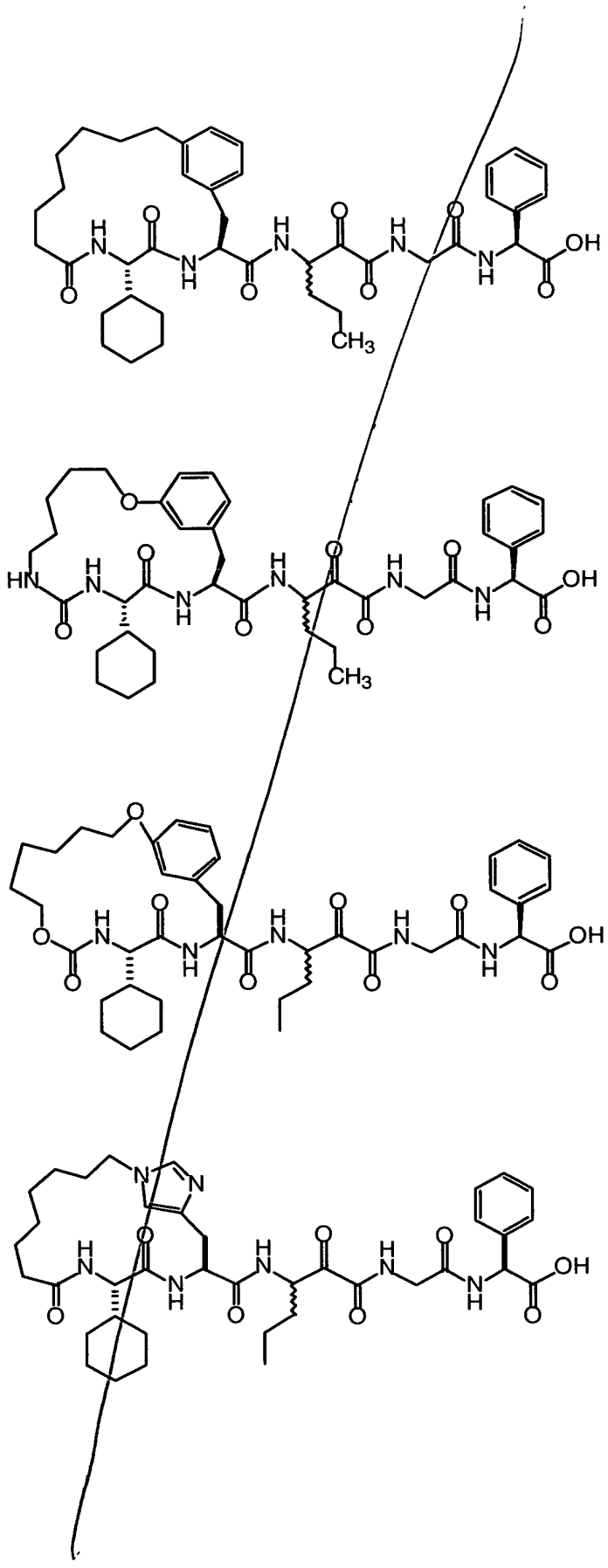
25. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV protease.

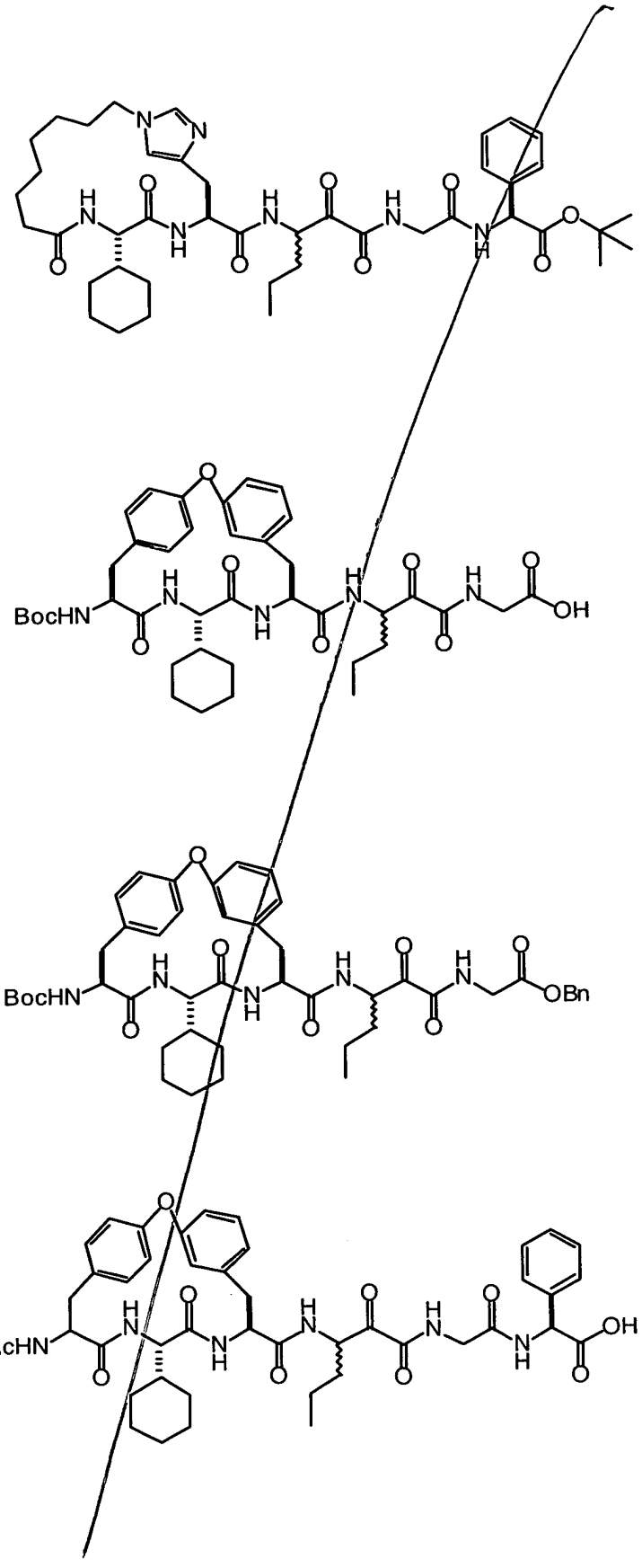
26. A method of preparing a pharmaceutical composition for treating disorders associated with the HCV protease, said method comprising bringing into intimate contact a compound of claim 1 and a pharmaceutically acceptable carrier.

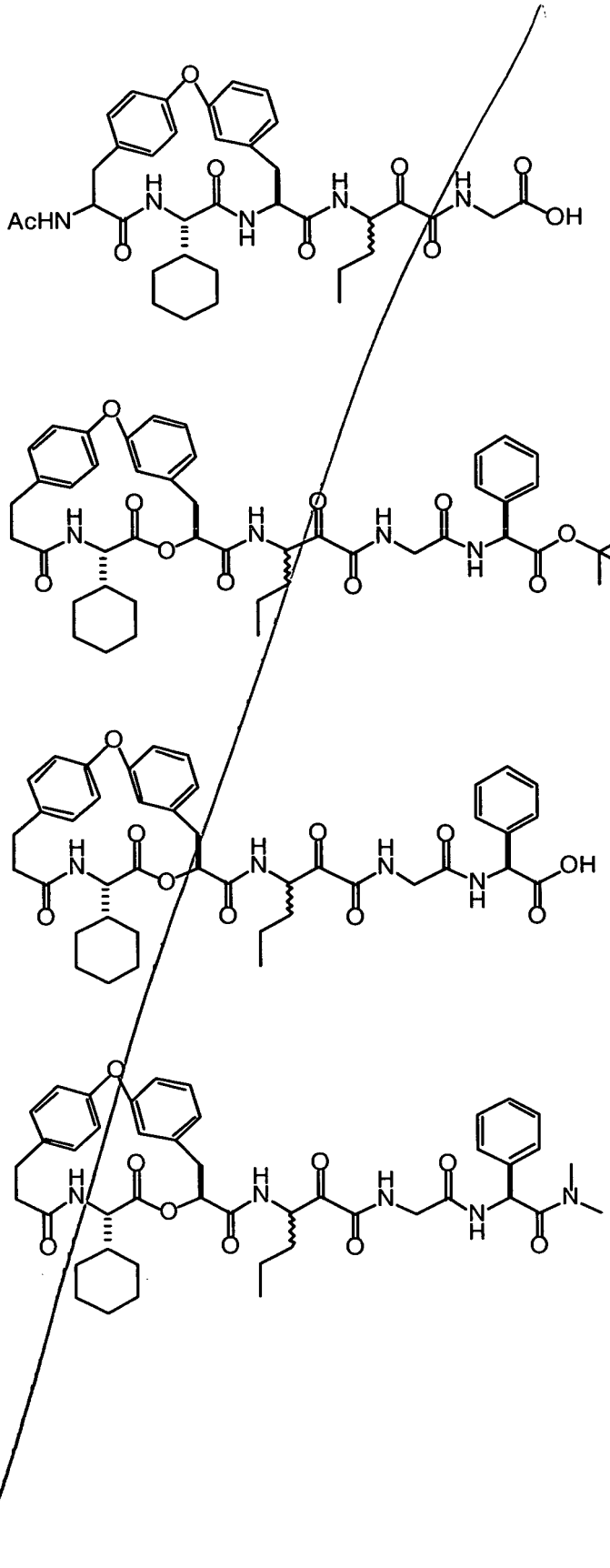
27. A compound exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers, rotamers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the group of compounds with structures listed below:

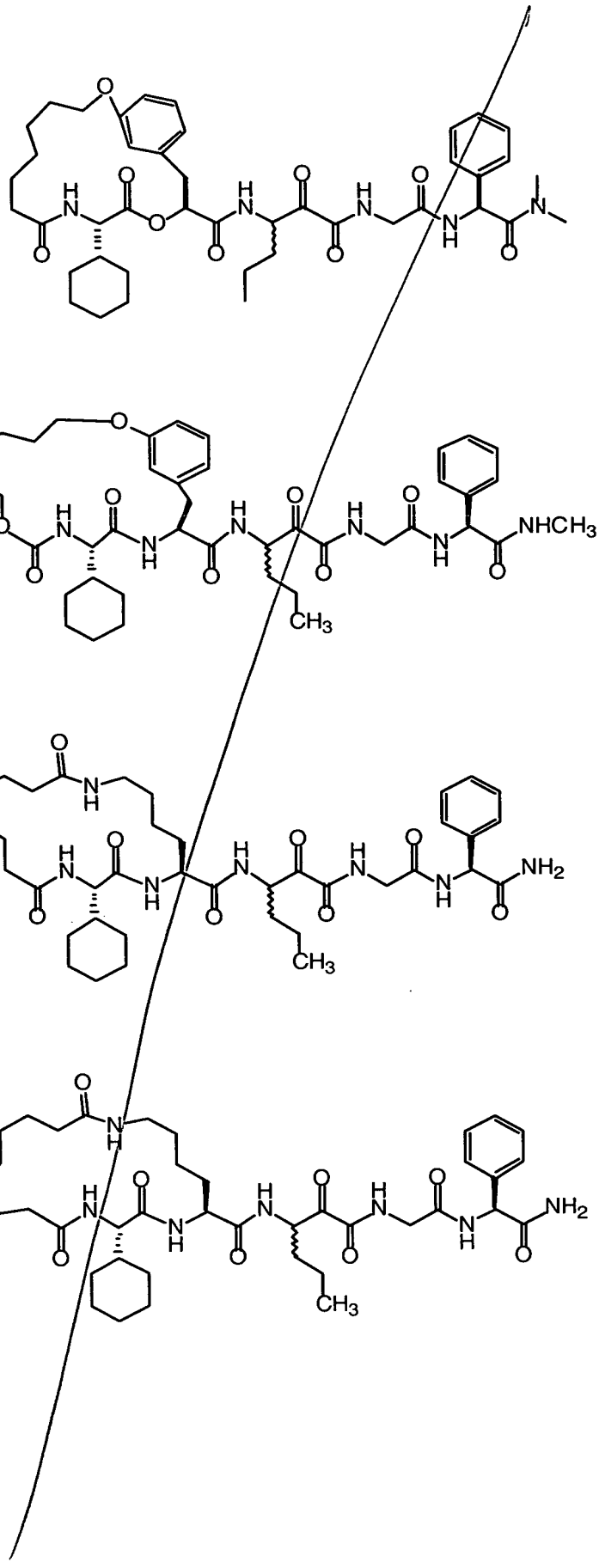


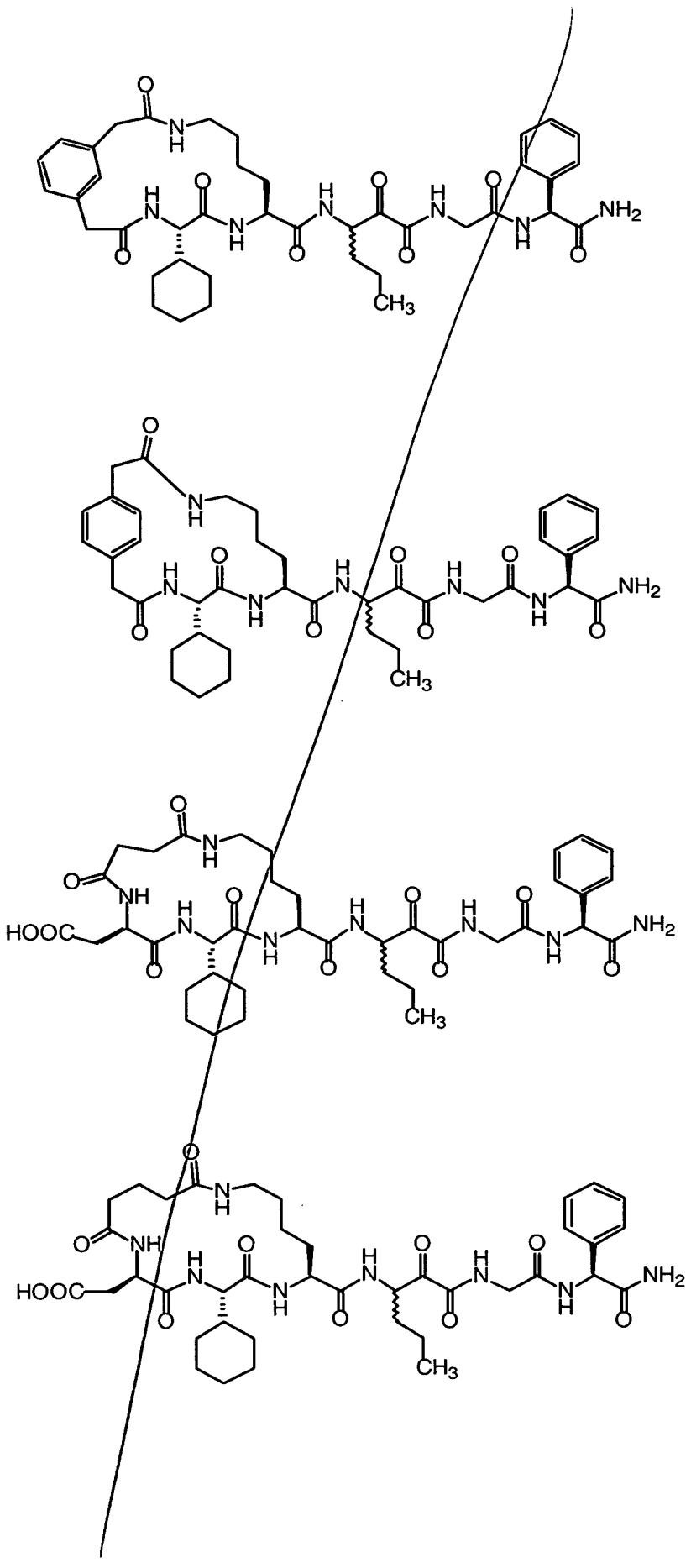


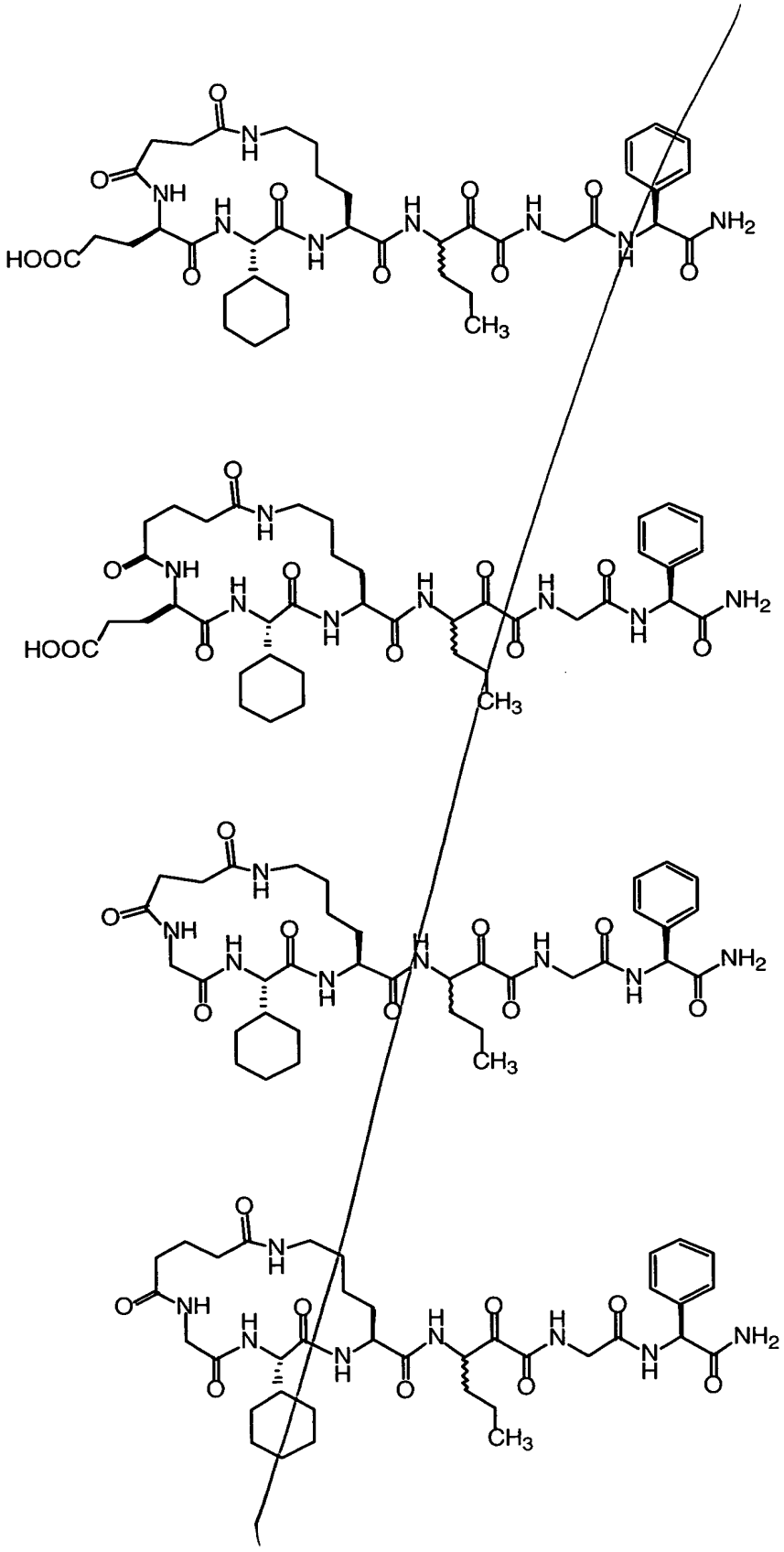



BocHN
OH
BocHN
OBn
AcHN
OH


AcHN
OH
OH


NHCH3
CH3
NH2
CH3
NH2
CH3




HOOC
NH
NH
NH

28. A pharmaceutical composition for treating disorders associated with the HCV protease, said composition comprising therapeutically effective amount of one or more compounds in claim 27 and a pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28, additionally containing an antiviral agent.

30. The pharmaceutical composition of claim 28 or claim 29, still additionally containing an interferon.

31. The pharmaceutical composition of claim 30, wherein said antiviral agent is ribavirin and said interferon is α-interferon.

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